ties are not extensive and they heavily rely on the avidity of bivalent IgG molecules to attain potent binding (~nM K_D).

SUMMARY

[0008] Treatment of influenza A virus (JAY) and the development of vaccines that broadly protect against highly diverse influenza virus serotypes are of clinical interest, but a significant challenge for vaccine development is defining conserved epitopes that are capable of eliciting cross-reactive protective antibodies in these diverse viruses. Isolation of naturally-occurring broad-spectrum human mAbs to IAV as described herein provides for identification of critical epitopes for rational design of structure-based broadly protective influenza vaccines.

[0009] Antibodies disclosed herein recognize an HA head domain epitope at the trimer interface, which site appears to be parallel but not overlapping with the receptor binding site. The epitope is a highly conserved site of vulnerability that is hidden in the HA trimer interface, which more pronounced in the HA0 form of the trimer. The antibodies show excellent binding affinity to diverse serotypes. A feature of this class of antibodies is mediation of ADCC activity and in vivo protection against major influenza subtypes that are pathogenic for humans, providing utility as a broad-spectrum antiviral therapeutic against various IAV infections. Embodiments of the invention include isolated antibodies and derivatives and fragments thereof, pharmaceutical formulations comprising one or more of the human anti-influenza virus monoclonal antibodies; and cell lines that produce these monoclonal antibodies. Also included are antigenic compositions comprising the HA trimer interface epitope presented in an immunogenic format.

[0010] In accordance with the present disclosure, a method of detecting an influenza A virus infection in a subject is provided, comprising (a) contacting a sample from said subject with one or a combination of antibodies or antibody fragments having clone-paired heavy and light chain CDR sequences from Tables 3 and 4, respectively; and (b) detecting influenza A virus in said sample by binding of said antibody or antibody fragment to an influenza A virus hemagglutinin in said sample. The sample may be a body fluid, such as blood, sputum, tears, saliva, mucous or serum, semen, cervical or vaginal secretions, amniotic fluid, placental tissues, urine, exudate, transudate, tissue scrapings or feces. Detection may comprise ELISA, RIA, lateral flow assay or western blot. The method may further comprising performing steps (a) and (b) a second time and determining a change in influenza A virus hemagglutinin levels as compared to the first assay.

[0011] The one or a combination of antibodies or antibody fragments may be encoded by clone-paired variable sequences as set forth in Table 1; may be encoded by light and heavy chain variable sequences having 70%, 80%, or 90% identity to clone-paired variable sequences as set forth in Table 1; or may be encoded by light and heavy chain variable sequences having 95% identity to clone-paired sequences as set forth in Table 1. An antibody or antibody fragment may comprise light and heavy chain variable sequences according to clone-paired sequences from Table 2; may comprise light and heavy chain variable sequences having 70%, 80% or 90% identity to clone-paired sequences from Table 2; or may comprise light and heavy chain variable sequences having 95% identity to clone-paired sequences from Table 2. The antibody fragment may be a recombinant scFv (single chain fragment variable) antibody, Fab fragment, $F(ab')_2$ fragment, or Fv fragment.

[0012] In another embodiment, there is provided a method of treating a subject infected with influenza A virus or reducing the likelihood of infection of a subject at risk of contracting influenza A virus, comprising delivering to said subject one or a combination of antibodies or antibody fragments having clone-paired heavy and light chain CDR sequences from Tables 3 and 4, respectively. An antibody or antibody fragment may be encoded by clone-paired variable sequences as set forth in Table 1; may be encoded by light and heavy chain variable sequences having 70%, 80%, or 90% identity to clone-paired variable sequences as set forth in Table 1; or may be encoded by light and heavy chain variable sequences having 95% identity to clone-paired sequences as set forth in Table 1. An antibody or antibody fragment may comprise light and heavy chain variable sequences according to clone-paired sequences from Table 2; may comprise light and heavy chain variable sequences having 70%, 80% or 90% identity to clone-paired sequences from Table 2; or may comprise light and heavy chain variable sequences having 95% identity to clone-paired sequences from Table 2. An antibody fragment may be a recombinant scFv (single chain fragment variable) antibody, Fab fragment, $F(ab')_2$ fragment, or Fv fragment. The antibody may be an IgG, or a recombinant IgG antibody or antibody fragment comprising an Fc portion mutated to alter (eliminate or enhance) FcR interactions, to increase half-life and/or increase therapeutic efficacy, such as a LALA, N297, GASD/ALIE, YTE or LS mutation or glycan modified to alter (eliminate or enhance) FcR interactions such as enzymatic or chemical addition or removal of glycans or expression in a cell line engineered with a defined glycosylating pattern. The antibody may be a chimeric antibody or a bispecific antibody.

[0013] The one or a combination of antibodies or antibody fragments may be administered prior to infection or after infection. The subject may be a pregnant female, a sexually active female, or a female undergoing fertility treatments. Delivering may comprise antibody or antibody fragment administration, or genetic delivery with an RNA or DNA sequence or vector encoding the antibody or antibody fragment.

[0014] In yet another embodiment, there is provided a monoclonal antibody, wherein the antibody or antibody fragment is characterized by clone-paired heavy and light chain CDR sequences from Tables 3 and 4, respectively. The antibody or antibody fragment may be encoded by clone-paired variable sequences as set forth in Table 1; may be encoded by light and heavy chain variable sequences having 70%, 80%, or 90% identity to clone-paired variable sequences as set forth in Table 1; or may be encoded by light and heavy chain variable sequences having 95% identity to clone-paired sequences as set forth in Table 1. The antibody or antibody fragment may comprise light and heavy chain variable sequences according to clone-paired sequences from Table 2; may comprise light and heavy chain variable sequences having 70%, 80% or 90% identity to clone-paired sequences from Table 2; or may comprise light and heavy chain variable sequences having 95% identity to clone-paired sequences from Table 2. The antibody fragment may be a recombinant scFv (single chain fragment variable) antibody, Fab fragment, $F(ab')_2$ fragment, or Fv fragment. The antibody may be an IgG, or a recombinant IgG antibody